REMARKS

Status of the Claims

Claims 1-4, 6, 7 and 10 are pending. Claims 1-4, 6, 7 and 10 are rejected. Claims 1, 4 and 10 are amended.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendments. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**". No new matter has been added. Reconsideration of the pending claims is respectfully requested.

Amendments to the claims

Claim 1 is amended to overcome the rejection of claims 1-3 under 35 U.S.C. §112, second paragraph, and the rejections under 35 U.S.C. §102(b) and §103(a). Claim 4 is amended to overcome the rejections under 35 U.S.C. §112, first paragraph, and the rejections under 35 U.S.C. §102(b) and §103(a). Claim 10 is amended to overcome the rejections under 35 U.S.C. §102(b). No new matter has been added.

The 35 U.S.C. §112, second paragraph rejections

The rejection of claims 1, 2 and 3 under 35 U.S.C. §112, second paragraph, is maintained because the claims are indefinite. Applicant respectfully traverses the rejection.

The Examiner maintains that claims 1 and dependent claims 2-3 are vague and indefinite in that claim 1 fails to recite what said animal is suffering from, and so it is not clear what result is to be achieved from administering basic fibroblast growth factor to said animal.

The Applicant respectfully submits that the amendment to claim 1 to recite "wherein said animal has endotoxic shock" removes the indefiniteness of claim 1 and therefore of dependent claims 2 and 3. Accordingly, the Applicant respectfully requests that the rejection of claims 1-3 under 35 U.S.C. §112, second paragraph, be withdrawn.

The 35 U.S.C. §102(b) rejections

The rejection of claims 1, 4 and 10 under 35 U.S.C. §102(b) as being anticipated by **Fuks** *et al.* (1994) was maintained. Applicant respectfully traverses the rejection.

The Examiner maintains that **Fuks** anticipates claim 1 because **Fuks** teaches the administration of basic fibroblast growth factor to an animal, and that although **Fuks** does not expressly teach that the administration of basic fibroblast growth factor leads to the inhibition of the generation of ceramide from sphingomyelin, this is an inherent property of the administration of basic fibroblast growth factor that cannot serve as a basis of patenting that process. Claim 1 only recites a new function, rather than a new use of the old basic fibroblast growth factor compound. Thus, according to the Examiner, with respect to claims 4 and 10, **Fuks** expressly teaches that administration of basic fibroblast growth factor to an animal inhibits endothelial apoptosis, so that **Fuks** also anticipates claims 4 and 10.

The Applicant respectfully submits that as amended, **Fuks** does not anticipate claim 1. **Fuks** teaches that administration of basic fibroblast growth factor to an animal inhibits radiation-induced endothelial apoptosis. The data in **Fuks** demonstrate that *in vitro*, basic fibroblast growth factor down-regulates apoptosis such that a greater percentage of cells survive at the lowest radiation doses applied (see Figure 1), corresponding to doses commonly used in the management of human tumors (see Discussion, page 2586). Therefore, **Fuks** aims to provide a way to increase the survival of

normal cells in radiation treatments in order to allow the use of higher therapeutic radiation doses, thus improving the ratio of killing cancer cells versus normal cells. Amended claim 1 recites a method of treating endotoxic shock comprising inhibiting the generation of ceramide from sphingomyelin, comprising the step of administering basic fibroblast growth factor to an animal that has endotoxic shock. **Fuks** does not teach, either expressly or inherently, that administration of basic fibroblast growth factor to an animal could be used to treat endotoxic shock. Amended claim 1 therefore recites a new use for basic fibroblast growth factor, i.e., to treat endotoxic shock.

The Applicant also respectfully submits that **Fuks** does not anticipate claims 4 and 10, for the same reasons as argued above. **Fuks** does not teach the administration of basic fibroblast growth factor as a method to treat endotoxic shock or sepsis. Therefore, in reciting methods of treating or preventing endotoxic shock or sepsis, amended claims 4 and 10 recite a new use for basic fibroblast growth factor that is not taught by **Fuks.**

Accordingly, because **Fuks** does not teach all of the elements of claims 1, 4 and 10 as amended, Applicant respectfully

requests that the rejection of claims 1, 4 and 10 under 35 U.S.C. §102(b) be withdrawn.

The 35 U.S.C. §103(a) rejection

The rejection of claims 1-4, 6 and 7 is maintained under 35 U.S.C. §103 as being unpatentable over **Fuks** *et al.* (1994). Applicant respectfully traverses this rejection.

The Examiner states that **Fuks** teaches a method of administering basic fibroblast growth factor to an animal to inhibit radiation-induced endothelial apoptosis, establishing a link between basic fibroblast growth factor administration and inhibition of endothelial apoptosis. Therefore, one of ordinary skill in the art would be motivated to practice the claimed method because many pathological conditions, such as endotoxic shock, lead to endothelial apoptosis. Pharmaceutical inventions are also considered useful at a stage of invention that is well before they are ready to be administered to humans, so that **Fuks** provides more than a mere "obvious to try" motivation.

Applicant respectfully maintains that claims 1-4, 6 and 7 are patentable over **Fuks** *et al.*, because **Fuks** contains no teaching

or suggestion that would motivate one skilled in the art to arrive at the instant invention with a reasonable expectation of success.

According to the present application, a major event in endotoxic shock is endothelial cell damage caused by bacterial lipopolysaccharide (LPS) (page 2, lines 5-11). Release of the inflammatory cytokine TNF-α initiates endothelial cell apoptosis mediated by the sphingomyelin pathway, which generates the second messenger ceramide (paragraph spanning pages 2-3). However, it was not known whether ceramide-mediated endothelial cell apoptosis plays a role in the LPS-induced endotoxic response in vivo (page 5, lines 10-13).

The present invention provides evidence that endotoxic shock results from disseminated endothelial cell apoptosis (page 6, lines 20-22), and that ceramide generation is an essential element in this process. The specification demonstrates that LPS induces endothelial apoptosis in mice, which can be blocked by an antibody against TNF-α (Figure 1); this apoptosis is accompanied by rapid ceramide generation (Figure 2). TNF-α also induces ceramide generation in mice (Figure 3), which can be blocked by anti-TNF-α antibody (Figure 4). Figure 5 additionally shows that mutant mice

deficient in acid sphingomyelinase, and therefore in ceramide generation, are defective in LPS-induced death. Basic fibroblast growth factor was known to protect endothelial cells from radiation-induced apoptosis from the teachings of **Fuks**. Accordingly, the specification demonstrates that endothelial cell damage is essential for the evolution of the endotoxic response by showing that basic fibroblast growth factor abrogated LPS-induced apoptosis in the endothelium of the intestine and lung of mice (page 27, lines 13-21, Figure 6A). Additionally, the site of basic fibroblast growth factor action was demonstrated to be the inhibition of ceramide generation from sphingomyelin. While basic fibroblast growth factor prevented ceramide elevation in response to LPS, serum levels of TNF-α were not affected (paragraph spanning page 27-28, Table II). Taken together, these data substantiate endothelial apoptosis as necessary for LPS-induced endotoxic shock, and define the protective effect of basic fibroblast growth factor as the inhibition of ceramide generation as part of TNF-α signaling. Thus, the specification provides evidence that LPS-induced endothelial apoptosis, like radiation-induced endothelial apoptosis, requires a functional sphingomyelin pathway (paragraph spanning page 25-26).

Amended claim 1 recites a method of treating endotoxic shock comprising inhibiting the generation of ceramide from sphingomyelin, comprising the step of administering b-FGF to an animal that has endotoxic shock. Claim 4 recites a method of treating endotoxic shock in an animal comprising inhibiting endothelial apoptosis, comprising the step of administering b-FGF to said animal. Dependent claim 6 provides that said animal is a human. Dependent claim 7 provides a dosage range and timing for basic fibroblast growth factor administration. **Fuks** teaches the administration of basic fibroblast growth factor to prevent apoptosis in endothelial cells sensitive to radiation-induced killing, and suggests that such administration could improve the efficacy of radiation therapy for the treatment of cancer. **Fuks** does not teach or suggest that basic fibroblast growth factor administration would be effective in treating endotoxic shock by inhibiting endothelial apoptosis.

A comparison between the teachings of **Fuks** and the disclosures in the present specification reveals that one skilled in the art would necessarily require the teachings of the specification to reasonably expect to succeed in practicing the claimed invention. In order to practice the claimed invention with the requisite expectation of success, one skilled in the art would require a teaching or

suggestion that endothelial apoptosis is essential to the endotoxic response, and that ceramide generation is essential for the development of endotoxic shock by LPS. Otherwise, the skilled artisan would not expect that basic fibroblast growth factor administration would serve as an effective treatment for endotoxic shock. **Fuks** teaches that basic fibroblast growth factor administration inhibits endothelial apoptosis, but no motivation is provided to attempt to use basic fibroblast growth factor administration as a treatment for endotoxic shock, without the teachings of the present specification. Therefore, the rejection of claims 1-4, 6 and 7 under 35 U.S.C. §103(a) as being unpatentable over **Fuks** amounts to an impermissible hindsight rejection. Accordingly, Applicant respectfully requests that this rejection be withdrawn in light of the claim amendments.

New Rejections

The 35 U.S.C. §112 rejection

Claims 4-7 and 10 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Applicant respectfully traverses this rejection.

The Examiner states that while the specification is enabling for a method of treating endotoxic shock and sepsis by administering basic fibroblast growth factor, wherein basic fibroblast growth factor *inhibits* endothelial apoptosis, it does not enable a method of treatment wherein basic fibroblast growth factor *prevents* endothelial apoptosis. Therefore, claims 4-7 and 10 are rejected in that they recite the prevention of endothelial apoptosis by basic fibroblast growth factor.

Applicant respectfully contends that the specification provides reasonable support for the claims as amended, and for the prevention of endothelial apoptosis in endotoxic shock by basic fibroblast growth factor. As claim 4 recites a method for treating endotoxic shock in an animal, claim 4 has been amended to recite "inhibits" rather than "prevents." Claim 10 recites a method of treating an individual at risk for sepsis by administering basic fibroblast growth factor, where basic fibroblast growth factor prevents endothelial apoptosis resulting from sepsis. An example of such prevention is shown by the specification on page 27, lines 1-21, and in Figures 6A-6B. When administered concomitantly with LPS, basic fibroblast growth factor was able to abrogate LPS-induced apoptosis in the intestine and lung of treated mice; such abrogation

was not total, but would necessarily involve substantial prevention of apoptosis in order to allow endothelial cell survival. Administration of basic fibroblast growth factor also enhanced the survival of LPS-treated mice, showing that basic fibroblast growth factor was effective in preventing the development of sepsis (Figure 6B). Accordingly, Applicant respectfully requests that the rejection of claims 4-7 and 10 under 35 U.S.C. §112, first paragraph, be withdrawn.

The 35 U.S.C. §102(e) rejection

Claims 4, 6 and 10 are rejected under 35 U.S.C. §102(e) as being anticipated by **Jain** *et al.* (U.S. Pat. No. 6,010,712). Applicant respectfully traverses this rejection.

The Examiner states that **Jain** discloses a method of treating sepsis by administering b-FGF to an animal suffering from sepsis. As claims 4, 6 and 10 are drawn to a method of treating endotoxic shock and sepsis in an animal by administering b-FGF to the animal, **Jain** anticipates these claims.

Applicant respectfully submits that **Jain** does not anticipate claims 4, 6 and 10, because the teachings of **Jain** do not include the inhibition of endothelial cell apoptosis in order to treat

endotoxic shock or sepsis. **Jain** provides no teaching or example linking the modulation of CAM expression by b-FGF to the inhibition of apoptosis in endothelial cells, nor any data to show that b-FGF administration would effectively treat endotoxic shock or sepsis. **Jain** only teaches that basic fibroblast growth factor decreases the cell surface expression of at least one of ICAM-1, VCAM-1 and E-selectin on endothelial cells, thereby decreasing adhesion of cytotoxic white cells to vascular endothelium. **Jain** makes no demonstration or suggestion that basic fibroblast growth factor treatment of endothelial cells would prevent apoptosis in these cells, only that the action of cytotoxic white cells would be inhibited. Therefore, all the elements of the present claims are not found among the teachings of **Jain**. Accordingly, Applicant respectfully requests that the rejection of claims 4, 6 and 10 under 35 U.S.C. §102(e) be withdrawn.

The 35 U.S.C. §103(a) rejection

Claims 4 and 7 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Jain** *et al.* Applicant respectfully traverses this rejection.

The Examiner states that although **Jain** does not disclose a method of administering basic fibroblast growth factor to an animal

using the specific doses and times recited in claim 7, it would have been obvious to one skilled in the art to optimize the dosage and duration of basic fibroblast growth factor given the teachings of **Jain** to administer basic fibroblast growth factor to an animal to treat sepsis, and that optimal dosage depends on weight, age and gender.

Applicant respectfully submits that the teachings of **Jain** do not provide sufficient motivation for one skilled in the art to combine the elements of the claimed invention. **Jain** discloses basic fibroblast growth factor dosages that have the purpose of decreasing the expression of CAMs on the surface of endothelial cells, to prevent adhesion and attack by cytotoxic white cells. These doses would not necessarily be effective to inhibit or prevent endothelial apoptosis by inhibiting the generation of ceramide from sphingomyelin. **Jain** also demonstrates that basic fibroblast growth factor decreases adhesion of activated natural killer cells to vascular endothelium *in vivo* using microgram amounts of basic fibroblast growth factor (30 µg b-FGF per mouse per cranial window; see column 5, lines 8-23. This dose is an order of magnitude higher than the dose used in the present application, which describes intravenous doses of nanogram amounts (800 ng) of basic fibroblast growth factor per mouse (see page 10, lines 9-17). The *in vivo* basic fibroblast growth factor dose taught by

Jain therefore does not suggest the much lower dose employed in the present application. Accordingly, because **Jain** does not provide a teaching or suggestion to motivate one skilled in the art to combine the elements of the claimed invention, Applicants respectfully request that the rejection of claims 4 and 7 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed December 13, 2002. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend claim 1 as follows:

1. (thrice amended) A method of treating endotoxic shock in an animal comprising inhibiting the generation of ceramide from sphingomyelin, comprising the step of:

administering basic fibroblast growth factor to ~~a n~~ said animal, wherein said animal has endotoxic shock.

Please amend claim 4 as follows:

4. (four times amended) A method of inhibiting endothelial apoptosis resulting from ~~treating~~ endotoxic shock in a n animal comprising ~~the step of administering basic fibroblast growth factor to said animal, wherein said fibroblast growth factor prevents endothelial apoptosis resulting from endotoxic shock by~~ inhibiting the generation of ceramide from sphingomyelin, comprising the step of:

administering basic fibroblast growth factor to said animal, wherein said animal has endotoxic shock.

Please amend claim 10 as follows:

10. (thrice amended) A method of treating an individual at risk for sepsis~~,~~ comprising inhibiting endothelial apoptosis resulting from sepsis by inhibiting the generation of ceramide from sphingomyelin, comprising the step of:

administering basic fibroblast growth factor to said individual, wherein said fibroblast growth factor prevents endothelial apoptosis resulting from sepsis.